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# COMPARISON OF TESTS OF THYROID FUNCTION*

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DIAGNOSIS in the field of thyroidology should rest, as in other areas of clinical medicine, primarily upon history and the physical examination of the patient. Having accomplished that, however, the doctor then has the duty and privilege of resorting to various laboratory aids to diagnosis. This evening for a few moments I will dwell upon what use we can make of certain of such procedures in gaining more complete knowledge of the nature of the morbid process in our patients with thyroid disorders, or in aiding us in the ruling of thyroid disorders in or out, in differential diagnosis.

I shall concern myself with three tests—BMR (basal metabolic rate), PBI (protein bound iodine of the blood serum), and RAI (the uptake of radio actively labelled iodine by the thyroid gland). The diagnostic significance of these tests, either singly or in combination‡, is what I shall hope to clarify.

There are other procedures useful in the area under discussion, such as the determination of serum cholesterol, creatine tolerance, thyro-

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‡ Having defined them, I shall in the remainder of the paper refer to the tests by these alphabetical designations.

tropin concentration in blood or urine, bone age, and others, but I have had relatively little experience with them and so shall not discuss them at this time. It is my belief also that the triad of tests which I first mentioned is the one on which chief dependence should be placed in estimating thyroid function for diagnostic purposes.

First let us consider, when we make any of the tests in question, precisely what it is that we are measuring: next, what significance measurement of this particular factor may have with respect to our diagnostic problem. BMR, PBI and RAI may all be accepted as in some degree tests of thyroid function, but they test different aspects of thyroid function, and therefore it should be clear that the question—which is the best of the lot—is irrelevant. What we really want to know is—what are the limitations of each?

BMR, the most venerable member of the triad, as ordinarily determined clinically, is nothing more than the determination of the amount of oxygen the subject takes up from the atmosphere per unit of time while in a state of physical, and if obtainable, mental rest, at normal room temperature, and eight or more hours after food. It is an index of how briskly the flame of life of the subject is burning at that particular moment. All activities of living animal tissue—protoplasm—eventually require oxygen. Even when a physiologic act takes place anaerobically an oxygen debt is acquired which must soon be paid off if the animal is to survive.

It is well known that the hormone of the thyroid importantly affects rate of bodily oxidation. Depriving the organism of thyroid by total thyroidectomy, or other destructive process, drops its oxidation rate by about 40 per cent. By feeding thyroid it can be raised even more than that. Ergo, BMR is a good index of thyroid function, but as we shall see presently, there are other factors than the secretory activity of the thyroid which can affect it. Moreover, what, one may ask, determines that portion of total respiratory metabolism, 60 per cent approximately, which takes place in the absence of the thyroid gland? This is an intriguing and fundamental question worthy of the attention of investigators, but perhaps not one which concerns us now as diagnosticians.

Having determined the basal oxygen absorption of an individual, we cannot use this information for diagnostic purposes without a suitable frame of reference. We cannot say the subject's metabolism is normal or abnormal without some method of comparing it with the metabolism of subjects known to be normal. The commonly employed procedure is to relate metabolism to surface area, and for practical purposes this is probably adequate. There are, however, certain theoretical objections to it. Before surface area formulae were available, body weight was used, but there was more variation between subjects of widely different shapes—tall-leans or short-fats—when weight was used as the reference point than when area was the criterion.

But neither weight nor area takes into consideration the ratio in any given subject between actual living protoplasmic mass, which is what determines metabolism, and inert tissue material such as fat, extracellular fluid, etc., which is metabolically inactive. An index of protoplasmic mass would seem to be the ideal criterion, but how can one measure that?

Years ago (1914), my then collaborators, W. W. Palmer and J. L. Gamble and I,[1] attempted to solve this problem by relating BMR to endogenous creatinine elimination. We did find a significant correlation, but being then not sufficiently fundamental in our orientation, we abandoned the method in favor of the Du Bois height-weight formula[2] which appeared shortly afterward. In the late thirties (1936-38), N. B. Talbot and his collaborators,[3-5] took up BMR and creatinine elimination again, and found as did we, a good correlation, but they also failed to develop their findings further. I have always regretted that we did not exploit the method more thoroughly.

I must not at this time belabor the theoretical aspects of BMR determinations any further. I merely want to indicate that it is desirable that when the diagnostician makes these measurements, he stop to think a bit about the nature of the thing he is measuring. With regard to thyroidal activity it seems to me permissible to say that BMR can be accepted as an index of the total impact of thyroid hormone upon its end-organs—that is to say upon all the cells of the body. If the sensitivity of end-organs remains constant, BMR is an index of the amount of thyroid hormone delivered to end-organs.

PBI, the second member of the triad, presents a simpler problem. It can be safely accepted as a tolerably dependable index of the level of thyroid hormone circulating in the blood, of hormone on its way from factory (thyroid gland) to consumer (the target cells). The height of this stream obviously is related to the activity of the thyroid gland, but in a different way than is BMR. The two could, theoretically at least, vary independently if a change should occur in the sensitivity of end-organs to thyroid hormone. It has been found also (Riggs[6]) that when the functional status of the thyroid gland changes rapidly, PBI parallels this change more promptly than does BMR. For example, what we call the Farquharson effect,[7] namely, the fall in cases of non-myxedematous hypometabolism when thyroid administration is stopped, to a level lower than the starting one, is more pronounced in the case of PBI than it is in that of BMR.

There is one important artefact that may intrude in PBI determination. The gall bladder dyes containing iodine hook into serum proteins and remain in the blood stream for months. They would be determined as PBI, and may cause an elevation of PBI which is not due to thyroxine. Indeed, if any patient has had cholecystography within a year, his PBI may not accurately reflect his blood level of thyroid hormone.

The last member of the triad, RAI, may be said to represent directly the thirstiness, or avidity, of the thyroid gland for iodine. It will be affected by the degree of stimulation of the thyroid, as for example, by its normal stimulator, the thyrotropic hormone of the pituitary, or thyrotropin, and by the capability of the gland to respond to stimulation. The latter can be affected by chemical agents which interfere with either the iodine trapping mechanism of thyroid cells or with the process of synthesis of thyroid hormone.

There are various methods of using labelled iodine for diagnostic purposes. One can give a so-called tracer dose of radiation and follow the uptake directly by Geiger counter over the gland, or one can collect urine and determine uptake by the thyroid indirectly on the assumption that the portion of the dose of radiation given which is not recovered in the urine is chiefly collected in the thyroid.[8] There are several variations of each of these approaches which I have not time to go into at present. One can if one wishes, follow RAI in thyroid gland, blood and urine simultaneously. Such studies are yielding some very comprehensive information on thyroid function. They are hardly at present, however, within the field of practical diagnosis.

I will now review certain formulae which have been obtained by this triad of tests in various types of thyroid disorders and in related conditions. In doing so I want to make it clear that I am not claiming that the use of all three tests has become mandatory for routine diagnostic purposes. PBI determinations are less available and more costly than those of BMR, and RAI uptakes are far less accessible and far more costly than either of the others. Moreover, both PBI and RAI determinations require much more highly trained personnel than does the time-honored and generally used BMR determination.

My point is, however, that if the three, or any two of them, can be had, a somewhat greater insight into the patient's status can be obtained than with any one of them alone. Particularly is this true in differential diagnosis. We may draw analogies with the role of tests of liver function in liver disease, or of kidney function in kidney disease. You have a whole battery of tests for each, but certainly don't need them all for routine purposes. Yet if you want a really penetrating understanding of what is going on in the diseased liver or kidney, you must have information on more than one aspect of its function.

Let us now get down to cases and see what different combinations of the three measurements we find in various diseases.

In Tables 1 and 2, I have given diagnoses and have indicated by arrows whether we may expect the BMR, PBI and RAI to be normal, elevated or depressed in each of the several conditions shown. It should be said at once that the direction of some of the arrows is based on rather scanty data and subject to change without notice. I have avoided numerical values, but will remind you that BMR may get as low as −45 per cent in total athyreosis and as high as +80 per cent in thyrotoxicosis. According to the method our laboratory uses, PBI in euthyroidism runs from 3.5 to 7.0 micrograms per cent, and in clinical thyrotoxicosis from 8. to 35 micrograms per cent. In clinical hypothyroidism it runs from 3.0 to 0.0 micrograms per cent. RAI uptake in 48 hours, as we find it, runs in euthyroidism from 20 per cent to 55 per cent of the administered dose; in hyperthyroidism from 60 per cent up, and in hypothyroidism from 15 per cent down.

In Table 1 we have first the normal or euthyroid state. In this by definition the tests are all normal—the arrows horizontal and double ended. Next are shown the direction the tests take in clinically definite thyroid diseases. It will be seen that in all such the BMR and PBI arrows point in the same direction. In the thyrotoxic or hyperthyroid states they point upward, in the hypothyroid, downward. This is quite what is to be expected. The RAI arrow also takes the same direction as the others except in two situations. In thyrotoxicosis persistent on iodine, of course, BMR and PBI are elevated, because by definition it is a state

TABLE I

| DIAGNOSIS | BMR | PBI (SERUM) | RAI (UPTAKE) |
|---|---|---|---|
| NORMAL OR EUTHYROID | ↔ | ↔ | ↔ |
| THYROTOXICOSIS OF GRAVES' DISEASE | ↑ | ↑ | ↑ |
| THYROID ADENOMA WITH HYPERTHYROIDISM | ↑ | ↑ | ↑ |
| HYPERTHYROIDISM PERSISTING ON IODINE | ↑ | ↑ | ↓ |
| HYPERTHYROIDISM FACTITIA | ↑ | ↑ | ↓ |
| HYPEROPHTHALMOPATHIC GRAVES' WITH EUTHYROIDISM | ↔ | ↔ | ↔ |
| PRIMARY MYXEDEMA | ↓ | ↓ | ↓ |
| PITUITARY MYXEDEMA | ↓ | ↓ | ↓ |
| IODINE WANT | ↔ | ↔ | ↑ |
| END-ORGAN INSENSITIVITY TO THYROID HORMONE (THEORETICAL) | ↓ | ↑ | ? |

when thyroid hyperfunction persists despite continuing treatment with iodine. However, if under such circumstances a tracer dose of RAI is given, very little will be taken up because the gland is already saturated with iodine. This same formula of BMR and PBI up, and RAI down, is found, so far as I know, only in one other condition, and in that it is close to pathognomonic. In thyrotoxicosis factitia, that is to say, thyrotoxicosis due to the ingestion of thyroid with or without doctor's orders, the BMR will be elevated because end-organs respond to an excess of hormone whether it be derived from the thyroid gland or the alimentary canal. PBI will be elevated in similar fashion. However, an excess of thyroid hormone in the blood suppresses the pituitary with respect to thyrotropin secretion, therefore in thyrotoxicosis factitia RAI uptake will be depressed. If you have a patient who is thyrotoxic, but with no goiter, no eye signs, and who denies taking thyroid, use the triad of tests and perhaps you can pin a diagnosis of thyrotoxicosis factitia on him by finding the formula BMR and PBI up and RAI down.[9]

In hyperophthalmopathic Graves' disease with euthyroidism the values of all three tests are normal.[10] Of those cases of Graves' in which the BMR swings to hypothyroid levels we have not as yet PBI and RAI data.

In primary thyroidal myxedema, as might be expected, all three values are down, and the same holds true in myxedema of pituitary origin, although the fall in PBI and RAI may be relatively less than that in BMR. I have indicated this in Table 1 by making the PBI and RAI arrows a little shorter.

In an endemic goiter area where iodine is scarce, the thyroid, by increasing its avidity for iodine maintains for a long time normal output of hormone, so that BMR and PBI would be normal, but if RAI is given, its uptake would be increased.

The last item in Table 1 is purely hypothetical. We have never established a diagnosis of insensitivity of end-organs to thyroid hormone. But such a condition may exist. It has been found in the case of parathyroids and gonads. It is well to be looking for it. What the test formula would be in such a condition, should it exist, is purely a matter for speculation. The BMR one might expect to be down, and if the thyroid gland attempted to compensate by overproduction of hormone, as in the castration phenomena, PBI and RAI would be up. But would the thyroid gland hyperfunction under such circumstances? Who can say?

At this point I can hear some of you murmuring—so what? Why bother with all this barrage of laboratory tests except in the rare case where one wishes to rule thyrotoxicosis factitia in or out? I will reply to that. Indeed there is no reason at all in clinically obvious cases. Any one of the tests is sufficient under such circumstances, or, if you are a good clinical observer, you can get on well without any of them. Symptoms and signs of the disease are sufficient in well developed cases. My reason for showering you with arrows, however, was to indicate the meaning of the different measurements so that they can really be helpful in borderline cases when diagnosis is not clear, and when you will get more help from two, or better three, of the tests than from one.

While BMR alone is what is generally relied on, as we shall see presently, there are several non-thyroid factors which may shift it up or down and make it difficult to interpret except when other evidence is available. In borderline hyper or hypothyroid situations, either PBI or RAI is more dependable as a diagnostic aid than BMR. There is some difference of opinion among authorities of which of the first two has the greater diagnostic significance in this connection. Of recent years we have not infrequently been able to establish a diagnosis of

TABLE 2

| DIAGNOSIS | BMR | PBI (SERUM) | RAI (UPTAKE) |
|---|---|---|---|
| ANOREXIA NERVOSA | ↓ | ↓ | ↓ |
| STARVATION | ↓ | ↓ | ↓ |
| NON-MYXEDEMATOUS HYPOMETABOLISM | ↓ | ↔ | ↔ |
| HYPERMETABOLISM WITHOUT THYROTOXICOSIS | ↑ | ↔ | ↔ |
| DINITROPHENOL POISONING | ↑ | ↓ | ↔ |
| NEPHROSIS | ↓ | ↓ | ↔ |
| PREGNANCY | ↑ | ↑ | ? |
| PHAEOCHROMOCYTOMA | ↑ | ↔ | ↔ |
| LEUKEMIA | ↑ | ↔ | ↔ |
| ADDISON'S DISEASE | ↓ | ↔ | ↔ |

hyperthyroidism in persons with BMR within the standard range by finding significant elevations in either PBI, RAI or both.

In Table 2, I have shown the directional tendencies in certain non-thyroidal states which may enter into differential diagnosis. In anorexia nervosa and in starvation, the two states presumably being identical so far as endocrine balance goes, we get formulae quite like those in pituitary myxedema. In the last mentioned hypopituitarism results from actual destruction of the anterior lobe; in the others it is underactive, we believe from inanition.

Hypometabolism with no clinical evidence of thyroid disease, in our experience, has shown normal PBI and RAI. Just what these cases represent physiologically I don't know. It has been suggested that they are examples of end-organ insensitivity, but I do not find that hypothesis altogether convincing. Dr. Silver has been good enough to tell me of his observations on hypermetabolism without evidence of thyroid disease. They also show no alteration in PBI and RAI. I have included them in Table 2 and hope Dr. Silver will comment.

In Dinitrophenol poisoning there is a terrific elevation of metabolism which is clearly not related to thyroid function. Chaikoff et al[11] have found the RAI normal and the PBI depressed in rats. Why the latter, is not clear. What the lowered BMR of nephrosis represents, I don't know. It is usually accompanied by lowered PBI, but a few observations do not show depression of RAI. Pregnancy is accompanied by a rise in BMR and in PBI. We have no observations in RAI in normal pregnant women. The situation here is to be regarded as a genuine increase in thyroid function. Physiological hyperthyroidism, so to speak.

The formula in pheochromocytoma is of great interest, and of much importance in differential diagnosis. In this condition there is no hyperthyroidism but there is hypermetabolism due to an excess of another calorigenic hormone, adrenaline. This raises BMR but not PBI or RAI.

A similar formula is to be found in leukemia, but the mechanism involved is more obscure. Finally, in Addison's disease there characteristically is lowering of BMR but not of PBI or RAI.

In conclusion I may say that after the diagnostic possibilities of history and physical examination in suspected thyroid cases have been exhausted, use may be made of any or all of the laboratory tests mentioned. At times they will add to the understanding of the case and clarify points in differential diagnosis in an outstanding manner. When we make use of them it is well that we bear in mind just what it is we are measuring, and what the special significance of the finding may be and the limitations of each of the several methods.

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